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Prediction for survival following docetaxel-based chemotherapy in Taiwanese men with castration-resistant metastatic prostate cancer

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ABSTRACT

Introduction: Docetaxel-based chemotherapy has been demonstrated to improve survival in patients with metastatic castration-resistant prostate cancer (mCRPC). The aim of this study is to analyze the possible prognostic factors associated with survival and to attract physicians' attention to high-risk patients.

Material and methods: Thirty-nine consecutive patients with mCRPC who received docetaxel-based chemotherapy between July 2007 and November 2013 were enrolled in this study. The Kaplan–Meier curve was used to assess the association between prostate-specific antigen (PSA) response (defined as PSA level decreases $\geq 50\%$), and overall survival and cancer-specific survival. Cox regression analysis was performed to identify the independent significant predictors of overall survival and cancer-specific survival.

Results: Twenty-one of the 39 patients (54%) experienced PSA response and the median overall survival was 13.51 months (range, 3–43 months). Patients with PSA response had longer time to PSA nadir level compared with patients without PSA response ($p = 0.010$). PSA response was an independent factor of overall survival and cancer-specific survival from Cox regression analysis ($p = 0.014$ and $p = 0.05$, respectively). In both univariate and multivariate analysis, cycles of chemotherapy, time to PSA nadir, and time to PSA progression were significant predictors for overall survival.

Conclusion: The present study showed that PSA response demonstrated significance as a predictor for clinical outcome. However, Charlson comorbidity index (CCI) is not related to survival. A further prospective analysis is warranted.

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1. Introduction

Prostate cancer (PCa) is the second most common malignancy in men worldwide and is the sixth leading cause of death with 258,000 deaths annually.¹ Although the incidence rate and mortality rate of PCa in Asia are lower than in Western societies, it has been increasing in Asian men including Taiwanese men within recent years.² For localized prostate cancer, treatment including radiotherapy or surgery can control the tumor burden efficiently and present excellent disease outcome. However, for some it can

become an advanced or metastatic disease.³ For these patients, androgen deprivation therapy (ADT) is the initial choice of treatment when PCa is under a hormone sensitive state. The tumor can regress while serum prostate-specific antigen (PSA) will decline after ADT, which also alleviates symptoms of disease such as bone pain.⁴ Nevertheless, metastatic PCa will become resistant to ADT and be renamed to metastatic castration-resistant prostate cancer (mCRPC) after an average of 2 years.⁵

Since the two large completed Phase III randomized control trials of SWOG 99-16⁶ and TAX 327⁷ demonstrated the role of chemotherapy in mCRPC in 2004, docetaxel-based chemotherapy has been regarded as the main system of management that presents significant survival benefits. In the past 5 years, several novel treatments have been studied in Phase III clinical trials for patients not suitable for or resistant to docetaxel. Although it needs further

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research due to not being curative, it still proposes another treatment option for mCRPC patients.⁸

Many previous studies have demonstrated that reductions in PSA of at least 50% from baseline can present improved survival and is considered to be a marker of response in patients after receiving systemic therapy.⁹ The purpose of this study was to evaluate the influence of PSA kinetics in survival outcome and to identify other possible prognostic factors including Charlson comorbidity index (CCI) in Taiwanese men with mCRPC.

2. Materials and methods

The present study included 39 consecutive patients with mCRPC who received docetaxel-based chemotherapy between July 2007 and November 2013 in Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. All patients were confirmed as having prostate adenocarcinoma histologically with metastasis upon imaging including computed tomography, magnetic resonance imaging, or bone scans, and disease progression despite androgen deprivation therapy with no previous treatment of chemotherapy. Three sequential increases in serum PSA level with castration levels of serum testosterone ($< 50 \text{ ng dL}^{-1}$) was recognized as mCRPC. This study was approved by the Institutional Review Board of our institution.

The therapeutic schedule in our institution consisted of docetaxel 70 mg/m^2 over 60 minutes through intravenous infusion on a 28-day cycle, plus oral prednisolone (5 mg) twice daily for 5 days (Days 1–5). We retrospectively evaluated data with various parameters including patient characteristics during chemotherapy (age, serum PSA level, hemoglobin level, serum PSA nadir, time to PSA nadir, time to progression, cycles of chemotherapy, and Charlson scores). After the beginning every cycle of chemotherapy, serum PSA level was checked combined with complete blood count, and renal and liver functions. PSA response was defined as a reduction of at least 50% from the baseline levels for at least 4 weeks. PSA nadir is the lowest point of serum PSA level, and the time to PSA nadir means the duration from the initial chemotherapy to PSA nadir level. The definition of PSA progression is more than a 50% rise from the PSA nadir and an elevation in the absolute PSA level by at least 5 ng/mL confirmed after at least 1 week.¹⁰ The time to PSA progression was calculated between chemotherapy initiation and PSA progression. The Charlson scores were calculated according to the Charlson comorbidity index (CCI), where weighted scores of 19 comorbidities equal to 1, 2, 3, and 6 based on the severity of the condition.¹¹ The overall survival was defined as the interval from the first docetaxel administration to the date of death.

After dividing patients into PSA response and no response, The Student *t* test was used to compare continuous variables. By using the Kaplan–Meier method, overall survival and prostate-specific survival probabilities were analyzed and compared between the two groups using the log-rank test. The related factors to overall survival were established by univariate and multivariate analyses using Cox regression hazard regression models. Because the number of cases is limited, candidate variables were selected from univariate analysis within $p < 0.1$, then multivariate analysis was calculated with forward selection. A p value < 0.05 was considered statistically significant. All statistical tests were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA).

3. Results

The characteristics and treatment response of the 39 patients are summarized in Table 1. The median age in the initial chemotherapy was 72 years (range, 54–88 years) and the median number

Table 1
Characteristics of the patients.

Characteristics	
Number	39
Age (y)	72.08 \pm 9.31 (54–88)
Number of cycles	6.72 \pm 2.77 (2–14)
Serum PSA (ng/mL)	386.82 \pm 723.40 (5.28–3855.51)
Hgb (g/dL)	10.89 \pm 1.66 (7.50–13.80)
Metastatic site(s)	
Bone	36 (92)
Lymph node	17 (43.6)
Viscera	4 (10)
Lung	1 (2.5)
Liver	2 (5)
Brain	1 (2.5)
PSA response	21 (54)
PSA never decrease	6 (15)
PSA nadir (ng/mL)	88.33 \pm 112.00 (0.54–448.59)
Time to PSA nadir (mo)	4.30 \pm 3.54 (0.50–13.00)
Time to PSA progression (m)	5.14 \pm 5.39 (0.00–23.00)
Survival time after chemotherapy (m)	13.51 \pm 9.69 (3–43)
CCI scores (scores)	9.62 \pm 1.84 (7–17)
Death	22 (56)

Data are presented as *n* (%) or median \pm SD.

CCI = Charlson comorbidity index; Hgb = hemoglobin; PSA = prostate-specific antigen.

of cycles patients received was six, ranging from two cycles to 14 cycles. During follow-up, 22 of the 39 patients (56%) died. At the start of docetaxel chemotherapy, the median serum PSA level was 386.82 ng/mL (range, 5.28–3855.51 ng/mL) and the hemoglobin concentration was 10.89 g/dL (range, 7.50–13.80 g/dL). Among eligible patients the median Charlson scores, which were calculated according to their comorbidity condition, was 9.62 points (range, 7–17 points). All patients had metastatic disease and the most common metastatic site of all patients was bone, then subsequently, lymph nodes. During courses of chemotherapy, the median PSA nadir level and the median time to PSA nadir were 88.33 ng/mL (range, 0.54–448.59 ng/mL) and 4.30 months (range, 0.5–13 months) respectively. Twenty-one of the 39 patients (54%) experienced PSA response; however, six patients still presented PSA rising even after receiving chemotherapy. The median overall survival was 13.51 months (range, 3–43 months). Median time from treatment initiation to PSA progression was 5.14 months (range, 0–23 months).

After dividing patients into PSA response and no response groups, we analyzed the possible predictors for PSA response in Table 2. A significant difference in the PSA response in favor of the longer time to PSA nadir level was noted ($p = 0.010$). The receiver-operating characteristic curve of the time to PSA nadir to PSA response is in Fig. 1 and the cut-off value to predict PSA response is 1.5 months (sensitivity: 95%, specificity: 50%). Kaplan–Meier analysis, as shown in Figs. 2 and 3, demonstrated that PSA response is a significant factor for longer overall survival and cancer-specific survival ($p = 0.014$ and $p = 0.05$, respectively). From the results of univariate and multivariate analyses since the beginning of chemotherapy in Tables 3 and 4, cycles of chemotherapy, time to PSA nadir level, and time to PSA progression were independent predictors of overall and cancer-specific survival with all at $p < 0.05$.

4. Discussion

As the high incidence of PCa in the world is noted and the risk of progression to invasive PCa increases with age, many studies are dedicated to unveiling relevant knowledge of PCa in various ways. Since the validated evidence of the screening test for PSA level,

Table 2

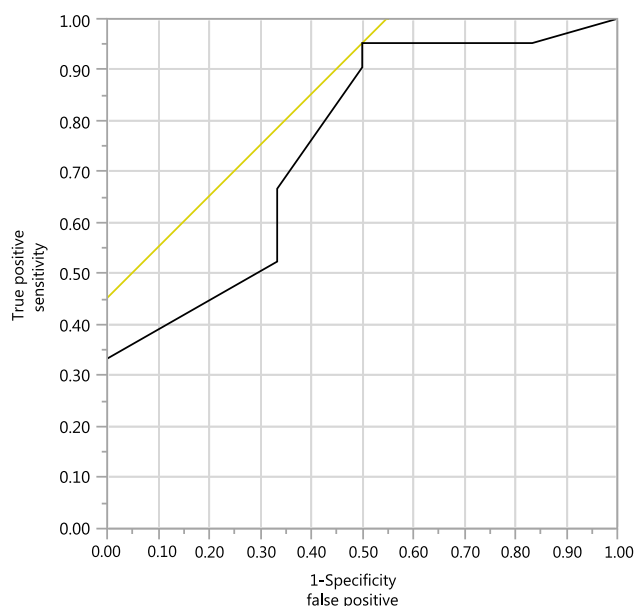
Association of factors between PSA response and no response.

	PSA response (n = 21)	PSA no response (n = 18)	p
Age (y)	71.48 ± 9.26	72.78 ± 9.59	0.669
Hgb (g/dL)	10.52 ± 1.46	11.32 ± 1.80	0.133
PSA level (ng/mL)	577.98 ± 937.24	163.79 ± 196.24	0.061
PSA nadir (ng/mL)	79.00 ± 98.97	104.64 ± 135.02	0.536
Time to PSA nadir (m)	5.33 ± 3.80	2.50 ± 2.14	0.010*
Number of cycles	7.29 ± 3.07	6.06 ± 2.29	0.170
Time to PSA progression (m)	5.31 ± 5.85	4.83 ± 4.71	0.812
CCI scores	9.67 ± 2.20	9.56 ± 1.38	0.854

Data are presented as mean ± SD.

* $p < 0.05$.

CCI = Charlson comorbidity index; Hgb = hemoglobin; PSA = prostate-specific antigen.

**Fig. 1.** ROC curve of the time to prostate-specific antigen (PSA) nadir to PSA response.

patient numbers who have been diagnosed with advanced stages have declined due to early detection of PCa.¹² However, in spite of improvement of the screening test, PCa continues to evidence high mortality rate in men, especially in US men, ultimately due to castration-resistant status.¹² In the present retrospective study, we assessed prognostic factors of overall survival and cancer-specific survival in patients with mCRPC under docetaxel-based chemotherapy as in Western society.

In our institution, we performed four-weekly docetaxel administrations of 70 mg/m² in combination with prednisolone for 5 days from the initiation of every course of chemotherapy. Compared with Kawahara et al.¹³ who performed chemotherapy of 55 mg/m² every 3–4 weeks with median overall survival time of 20.1 months, our study did not achieve this length; however, their study showed a median serum PSA level of 161 ng/mL lower than that of 386.82 ng/mL in our study. The PSA response in our study, comprised of 54% of all patients, was associated with better overall survival and cancer-specific survival. Some previous studies have demonstrated a PSA decline of either $\geq 30\%$ or $\geq 50\%$, which may be evidence of an early response of a cytotoxic agent with a reduction of tumor burden, and presents a strong association with survival.^{14–16}

In Table 2, it shows that the time to PSA nadir was the only prognostic factor to PSA response compared with those patients who did not achieve $\geq 50\%$ reduction of PSA. Our study suggests

that longer time to PSA nadir was associated with better PSA response. The mechanism is not clear, but Thomas et al.¹⁷ hypothesized that a rapid eradication of chemosensitive tumor cells may result in strengthening the growth of chemoresistant cells. According to both univariate and multivariate analyses for overall survival and cancer-specific survival in patients with mCRPC, time to PSA nadir also presents a significant prognostic factor. The association of shorter time to PSA nadir with poorer outcome of survival has been noted.

The number of cycles of chemotherapy was considered as a predictor for overall survival. However, the number of cycles the patients need to receive docetaxel-based chemotherapy is not confirmed. In our study, five patients received > 10 cycles of chemotherapy. Clinically, treatment may continue until adverse effects occur or disease progression, as in our institution. In a recent study Pond et al.¹⁸ found > 10 cycles may not enhance benefits but exposes more toxicity from retrospective analysis. Therefore, 10 cycles have generally become an acceptable duration of therapy worldwide. By contrast, in the Nishimura et al.¹⁹ analysis, selected patients in Japan showed a favorable response and delayed disease progression to longer durations of treatment. To prevent fatal toxicities from docetaxel and concomitant therapy, the condition of patients must be monitored carefully and regularly prophylactic drugs can be prescribed before initiation of chemotherapy. In our multivariate analysis, the longer duration of chemotherapy was related to higher overall survival and cancer-specific survival rates. The result is inconclusive, due to the small sample size. Moreover, according to our protocol, when the patient lives longer, he will receive more cycles of chemotherapy if the condition is still stable.

The comorbidity condition in patients may affect survival outcome and tolerance for toxicities. In order to clarify whether the comorbidity burden contributes as an independent prognostic factor for overall survival in mCRPC patients, we used the Charlson comorbidity index.²⁰ In our study, CCI score was not significantly independent to overall survival and cancer-specific survival of patients receiving docetaxel-based chemotherapy, and the result was the same as the analysis by Goyal et al.²⁰ A previous study still demonstrated CCI score had no association with overall survival in patients with locally advanced T3a prostate cancer.²¹ It is supposed that the difference in CCI scores between individuals is small in mCRPC patients, because it is at least six scores with distant metastases.

PSA level is generally considered to be related to tumor burden; therefore, PSA progression can present a negative impact to overall survival for mCRPC patients. As in Hussain et al.'s²² study, PSA progression was demonstrated as a significant prognostic factor of survival in patients of CRPC treated with chemotherapy. In our study, time to PSA progression was shown to be a predictor of overall survival and cancer-specific survival, which means longer time to PSA progression is associated with better survival outcome.

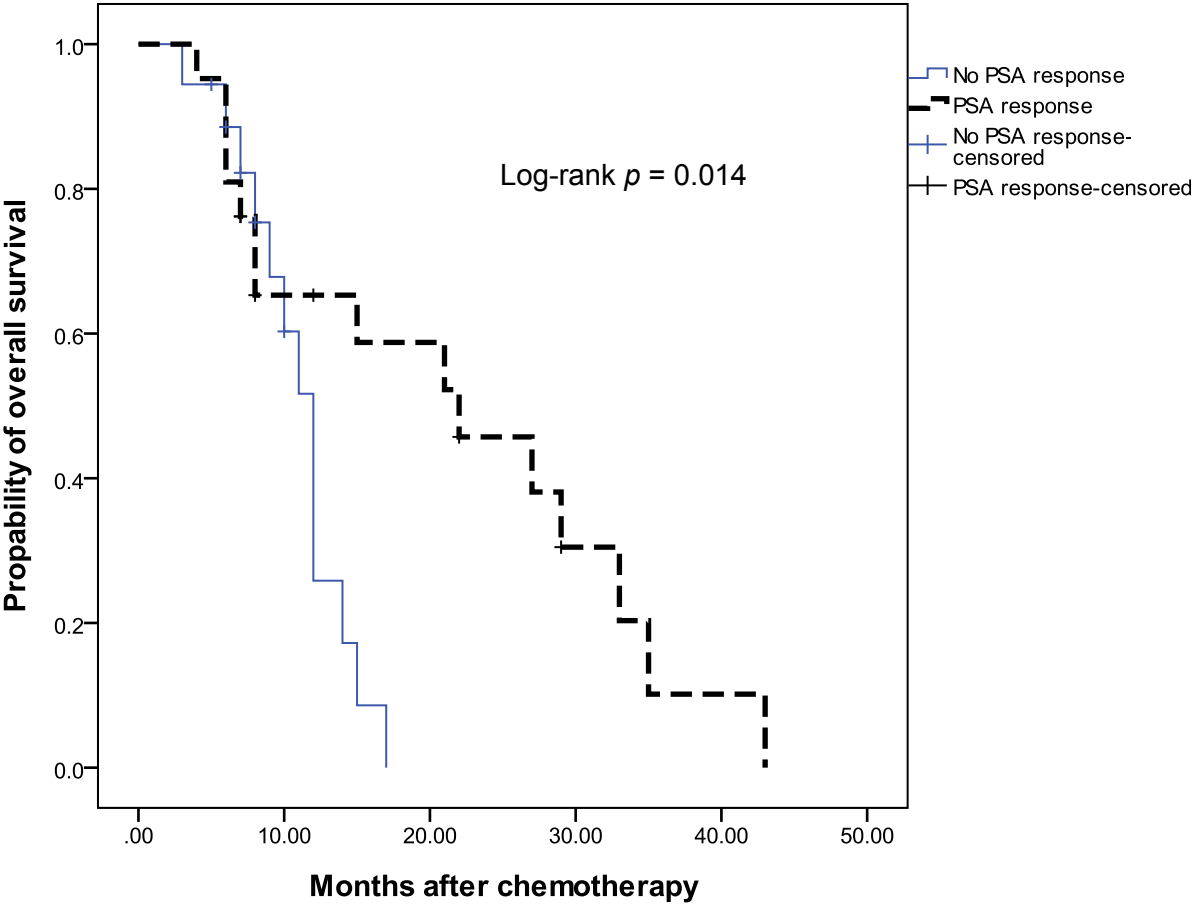


Fig. 2. Kaplan–Meier analysis of overall survival according to prostate-specific antigen (PSA) response status.

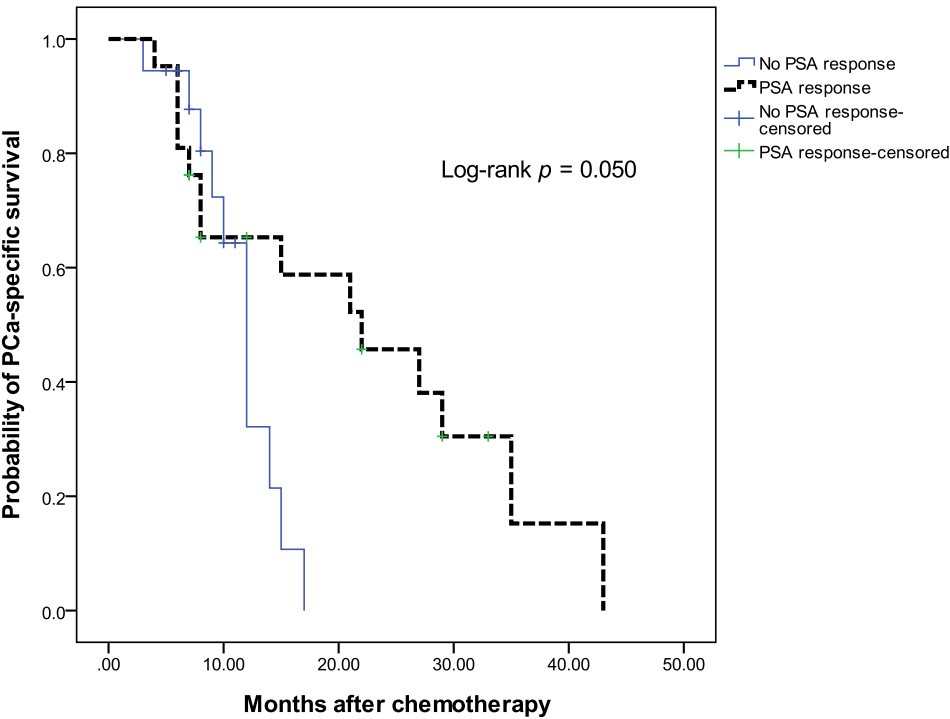


Fig. 3. Kaplan–Meier analysis of prostate cancer-specific survival according to prostate-specific antigen (PSA) response status.

Table 3

Association of baseline factors with overall survival by univariate and multivariate analysis.

Baseline characteristics	Univariate			Multivariate		
	HR	95% C.I.	p	HR	95% C.I.	p
Age (y)	1.011	(0.97, 1.05)	0.592			
Number of cycles	0.776	(0.65, 0.92)	0.004*	0.725	(0.60, 0.88)	0.001*
Hemoglobin (g/dL)	0.913	(0.72, 1.15)	0.444			
PSA level (ng/mL)	1.000	(1.00, 1.00)	0.563			
PSA nadir (ng/mL)	1.001	(1.00, 1.01)	0.416			
Time to PSA nadir (m)	0.714	(0.59, 0.87)	0.001*	0.708	(0.57, 0.87)	0.001*
Time to PSA progression (m)	0.915	(0.84, 1.00)	0.038*	0.844	(0.74, 0.96)	0.009*
CCI scores	1.155	(0.92, 1.45)	0.220			

* p < 0.05.

CCI = Charlson comorbidity index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

Table 4

Association of baseline factors with prostate cancer specific survival by univariate and multivariate analysis.

Baseline characteristics	Univariate			Multivariate		
	HR	95% C.I.	p	HR	95% C.I.	p
Age (y)	1.014	(0.97, 1.06)	0.548			
Number of cycles	0.773	(0.64, 0.93)	0.005*	0.723	(0.59, 0.88)	0.001*
Hemoglobin (g/dL)	0.884	(0.70, 1.12)	0.312			
PSA level (ng/mL)	1.000	(1.00, 1.00)	0.613			
PSA nadir (ng/mL)	1.001	(1.00, 1.01)	0.717			
Time to PSA nadir (m)	0.711	(0.58, 0.87)	0.001*	0.710	(0.57, 0.88)	0.002*
Time to PSA progression (m)	0.920	(0.84, 1.00)	0.050*	0.849	(0.75, 0.97)	0.014*
CCI scores	1.169	(0.92, 1.49)	0.209			

* p < 0.05.

CCI = Charlson comorbidity index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

There are some limitations of our study. One is that it was a retrospective study with heterogeneous patient backgrounds and a small sample size. Another is that the included variables may not be complete and lack other potential prognostic factors such as PSA doubling time, alkaline phosphatase, etc. A future prospective analysis needs to confirm and validate our results in larger samples of eligible patients.

5. Conclusion

This study demonstrated that PSA response, cycles of chemotherapy, time to PSA nadir, and time to PSA progression could present predictive factors of overall survival in Taiwanese patients with mCRPC. However, the CCI did not provide the association. In addition, time to PSA nadir was longer in PSA response patients compared with those without PSA response. These significant factors may take into account the treatment plan and decision-making after docetaxel-based chemotherapy for mCRPC patients.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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